NEWS 43 Feb 24 METADEX enhancements
NEWS 44 Feb 24 PCTGEN now available on STN
NEWS 45 Feb 24 TEMA now available on STN
NEWS 46 Feb 26 NTIS now allows simultaneous left and right truncation
NEWS 47 Feb 26 PCTFULL now contains images
NEWS 48 Mar 04 SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 49 Mar 19 APOLLIT offering free connect time in April 2003
NEWS 50 Mar 20 EVENTLINE will be removed from STN
NEWS 51 Mar 24 PATDPAFULL now available on STN
NEWS 52 Mar 24 Additional information for trade-named substances without structures available in REGISTRY
NEWS 53 Mar 24 Indexing from 1957 to 1966 added to records in CA/CAPLUS

NEWS EXPRESS January 6 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS INTER General Internet Information
NEWS LOGIN Welcome Banner and News Items
NEWS PHONE Direct Dial and Telecommunication Network Access to STN
NEWS WWW CAS World Wide Web Site (general information)

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* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 09:40:24 ON 01 APR 2003

=> e registry
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
The EXPAND command is used to look at the index in a file which has an index. This file does not have an index.

=>
Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?
Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> FILE REGISTRY

COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION

FULL ESTIMATED COST 0.21 0.21

FILE 'REGISTRY' ENTERED AT 09:40:42 ON 01 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 31 MAR 2003 HIGHEST RN 501072-24-8
DICTIONARY FILE UPDATES: 31 MAR 2003 HIGHEST RN 501072-24-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

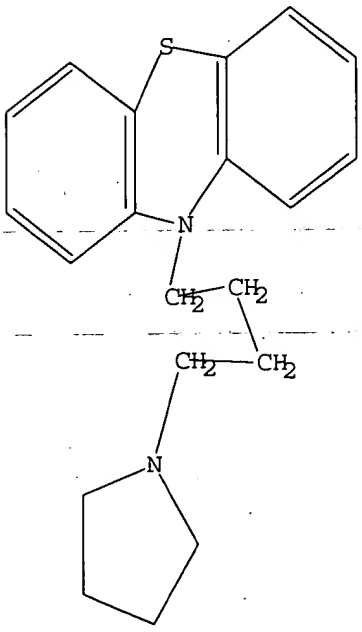
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09849400.1

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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=> s l1
SAMPLE SEARCH INITIATED 09:40:59 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     27 TO ITERATE

100.0% PROCESSED      27 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          229 TO      851
PROJECTED ANSWERS:               0 TO        0

L2             0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 09:41:10 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    611 TO ITERATE

100.0% PROCESSED     611 ITERATIONS                              11 ANSWERS
SEARCH TIME: 00.00.01

L3            11 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              148.15     148.36

FILE 'CAPLUS' ENTERED AT 09:41:22 ON 01 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 1 Apr 2003  VOL 138 ISS 14
FILE LAST UPDATED: 31 Mar 2003  (20030331/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

=> s l3
L4            20 L3

=> d l4 fbib histr abs total
```

'HISTR' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'

The following are valid formats:

ABS --------- GI and AB
ALL --------- BIB, AB, IND, RE
APPS -------- AI, PRAI
BIB --------- AN, plus Bibliographic Data and PI table (default)
CAN --------- List of CA abstract numbers without answer numbers
CBIB -------- AN, plus Compressed Bibliographic Data
DALL -------- ALL, delimited (end of each field identified)
DMAX -------- MAX, delimited for post-processing
FAM --------- AN, PI and PRAI in table, plus Patent Family data
FBIB -------- AN, BIB, plus Patent FAM
IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers;
SCAN must be entered on the same line as the DISPLAY,
e.g., D SCAN or DISPLAY SCAN)
STD --------- BIB, IPC, and NCL

IABS -------- ABS, indented with text labels
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
ISTD -------- STD, indented with text labels

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

HIT --------- Fields containing hit terms
HITIND ------ IC, ICA, ICI, NCL, CC and index field (ST and IT)
containing hit terms
HITRN ------- HIT RN and its text modification
HITSTR ------ HIT RN, its text modification, its CA index name, and
its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its
structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
OCC --------- Number of occurrence of hit term and field in which it occurs

To display a particular field or fields, enter the display field codes. For a list of the display field codes, enter HELP DFIELDS at an arrow prompt (=>). Examples of formats include: TI; TI,AU; BIB,ST; TI,IND; TI,SO. You may specify the format fields in any order and the information will be displayed in the same order as the format specification.

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ENTER DISPLAY FORMAT (BIB):BIB

L4 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2003:118638 CAPLUS
DN 138:153540
TI Preparation of aminobutylphenothiazines, -iminodibenzyls, and related compounds as chemosensitizing agents against chloroquine resistant plasmodium falciparum
IN Lin, Ai J.; Guan, Jian; Kyle, Dennis E.; Milhous, Wilbur K.
PA USA
SO U.S. Pat. Appl. Publ., 27 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2003032801	A1	20030213	US 2001-849400	20010507
PRAI US 2001-849400		20010507		

OS MARPAT 138:153540

L4 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2002:868744 CAPLUS
DN 137:370096
TI Tricyclic N-(aminoalkyl)-substituted phenothiazines, iminodibenzyls, iminostilbenes, and diphenylamines, active as chemosensitizing agents against chloroquine-resistant Plasmodium falciparum, and methods of making and using thereof
IN Lin, Ai J.; Guan, Jian; Kyle, Dennis E.; Milhous, Wilbur K.
PA United States Army Medical Research and Material Command, USA
SO PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002089810	A1	20021114	WO 2001-US14574	20010507

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI WO 2001-US14574 20010507
OS MARPAT 137:370096
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2002:372411 CAPLUS
DN 137:109247

TI Design, Synthesis, and Evaluation of New Chemosensitizers in Multi-Drug-Resistant Plasmodium falciparum
AU Guan, Jian; Kyle, Dennis E.; Gerena, Lucia; Zhang, Quan; Milhous, Wilbur K.; Lin, Ai J.
CS Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Silver Spring, MD, 20910, USA
SO Journal of Medicinal Chemistry (2002), 45(13), 2741-2748
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 137:109247
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2000:4293 CAPLUS
DN 132:273829
TI Relationship between cytotoxic activity and dipole moment for phthalimido- and chloroethyl-phenothiazines
AU Kurihara, Teruo; Motohashi, Noboru; Sakagami, Hiroshi; Molnar, Joseph
CS Faculty of Science, Josai University, Saitama, 350-0295, Japan
SO Anticancer Research (1999), 19(5B), 4081-4083
CODEN: ANTRD4; ISSN: 0250-7005
PB International Institute of Anticancer Research
DT Journal
LA English
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1999:654667 CAPLUS
DN 132:131770
TI Chemical structure and tumor type specificity of "half-mustard type" phenothiazines
AU Motohashi, Noboru; Kurihara, Teruo; Sakagami, Hiroshi; Szabo, Diana; Csuri, Klara; Molnar, Joseph
CS Department of Medicinal Chemistry, Meiji Pharmaceutical University, Tokyo, 204-8588, Japan
SO Anticancer Research (1999), 19(3A), 1859-1864
CODEN: ANTRD4; ISSN: 0250-7005
PB International Institute of Anticancer Research
DT Journal
LA English
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:282099 CAPLUS
DN 129:75984
TI The primary in vitro anticancer activity of "half-mustard type" phenothiazines in NCI's revised anticancer screening paradigm
AU Wuonola, Mark A.; Palfreyman, Michael G.; Motohashi, Noboru; Kawase, Masami; Gabay, Sabit; Gupta, Radha Raman; Molnar, Joseph
CS Scriptgen Pharmaceuticals, Inc., Medford, MA, 02155, USA
SO Anticancer Research (1998), 18(1A), 337-348
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research

DT Journal
LA English

L4 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:200671 CAPLUS
DN 128:265747
TI Correlation between structure and diverse biological activities of "half-mustard type" phenothiazines
AU Motohashi, Noboru; Kurihara, Teruo; Satoh, Kazue; Sakagami, Hiroshi; Molnar, Joseph
CS Department of Medicinal Chemistry, Meiji College of Pharmacy, Tokyo, 188, Japan
SO Anticancer Research (1997), 17(6D), 4403-4406
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English

L4 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:49717 CAPLUS
DN 128:162543
TI Drug resistance reversal, antimutagenicity and antiretroviral effect of phthalimido- and chloroethyl-phenothiazines
AU Motohashi, Noboru; Kurihara, Teruo; Kawase, Masami; Hever, Aniko; Tanaka, Masaru; Szabo, Diana; Nacsa, Janos; Yamanaka, Wataru; Kerim, Ablikim; Molnar, Joseph
CS Department of Medicinal Chemistry, Meiji College of Pharmacy, Tanashi, 188, Japan
SO Anticancer Research (1997), 17(5A), 3537-3543
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English

L4 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:49699 CAPLUS
DN 128:175800
TI The in vitro antitumor assay of "half-mustard type" phenothiazines in screens of AIDS-related leukemia and lymphomas
AU Wuonola, Mark A.; Palfreyman, Michael G.; Motohashi, Noboru; Kawase, Masami; Gabay, Sabit; Molnar, Joseph
CS SCRIPTGEN Pharmaceuticals, Inc., Medford, MA, 02155, USA
SO Anticancer Research (1997), 17(5A), 3425-3429
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English

L4 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:49698 CAPLUS
DN 128:162631
TI The primary in vitro antitumor screening of "half-mustard type" phenothiazines
AU Wuonola, Mark A.; Palfreyman, Michael G.; Motohashi, Noboru; Kawase, Masami; Gabay, Sabit; Nacsa, Janos; Molnar, Joseph
CS SCRIPTGEN Pharmaceuticals, Inc., Medford, MA, 02155, USA
SO Anticancer Research (1997), 17(5A), 3409-3423
CODEN: ANTRD4; ISSN: 0250-7005

PB Anticancer Research
DT Journal
LA English

L4 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1996:703922 CAPLUS
DN 126:26380
TI Synthesis and antitumor activity of 1-[2-(chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl]-1-ureas as potent anticancer agents
AU Motohashi, Noboru; Kawase, Masami; Kurihara, Teruo; Hever, Aniko; Nagy, Szilvia; Ocsocvszki, Imre; Tanaka, Masaru; Molnar, Joseph
CS Department Medicinal Chemistry, Meiji College Pharmacy, Tanashi, 188, Japan
SO Anticancer Research (1996), 16(5A), 2525-2532
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English

L4 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1996:518725 CAPLUS
DN 125:211824
TI Antitumor activity of phenothiazine-related compounds
AU Nagy, Sylvia; Argyelan, George; Molnar, Joseph; Kawase, Masami; Motohashi, Noboru
CS Faculty Medicine, Albert Szent-Gyorgyi Medical University, Szeged, H-6720, Hung.
SO Anticancer Research (1996), 16(4A), 1915-1918
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English

L4 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1996:472497 CAPLUS
DN 125:211925
TI Immunomodulating activities on cellular cytotoxicity and the blast transformation of human lymphocytes by 10-n-(phthalimido) alkyl-2-substituted-10H-phenothiazines and 1-(2-chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas
AU Petri, Ilidiko B.; Szekeres, Eva; Varga, Eva; Berek, Imre; Molnar, Joseph; Berek, Livia; Kawase, Masami; Motohashi, Noboru
CS Blood Transfusion Centre, Albert Szent-Gyorgyi Medical University, Szeged, H-6720, Hung.
SO Anticancer Research (1996), 16(3A), 1247-1250
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English

L4 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1996:239126 CAPLUS
DN 124:332043
TI Induction of DNA fragmentation in human myelogenous leukemic cell lines by phenothiazine-related compounds
AU Sakagami, Kiroshi; Takahashi, Hideo; Yoshida, Hiroshi; Yamamura, Mitsuhisa; Fukuchi, Kunihiko; Gomi, Kunihide; Motohashi, Noboru; Takeda, Minoru

CS School Medicine, Showa University, Tokyo, 142, Japan
SO Anticancer Research (1995), 15(6B), 2533-40
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English

L4 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1962:483298 CAPLUS
DN 57:83298
OREF 57:16630g-i,16631a-d
TI Dimethylaminophenothiazines
IN Craig, Paul N.
PA Smith Kline & French Laboratories
SO 4 pp.
DT Patent
LA Unavailable

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 3047572		19620731	US	19581210

L4 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1961:8225 CAPLUS
DN 55:8225
OREF 55:1667a-c
TI Basic alkylthioalkyl esters of phenothiazine-10-carboxylic acid and their salts
IN Myers, Gorden S.; Davis, Martin A.
PA American Home Products Corp.
DT Patent
LA Unavailable
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2951077		19600830	US	

L4 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1961:8224 CAPLUS
DN 55:8224
OREF 55:1666f-i,1667a
TI Methylenedioxy-substituted phenothiazines
IN Gordon, Maxwell
PA Smith, Kline & French Laboratories
DT Patent
LA Unavailable
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2945031		19600712	US	

L4 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1958:104438 CAPLUS
DN 52:104438
OREF 52:18502d-i,18503a-b
TI N-[(10-Phenothiazinyl)-lower alkyl]-1,5-iminocycloalkanes
IN Zenitz, Bernard L.
PA Sterling Drug Inc.
DT Patent

LA Unavailable
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2838505		19580610	US	

L4 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1957:73091 CAPLUS
DN 51:73091
OREF 51:13200a-d
TI Structure activity relationships of some phenothiazine-substituted nortropane derivatives
AU Long, J. P.; Lands, A. M.; Zenitz, B. L.
CS Sterling-Winthrop Inst., Rensselaer, NY
SO J. Pharmacol. Exptl. Therap. (1957), 119, 479-84
DT Journal
LA Unavailable

L4 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1957:73090 CAPLUS
DN 51:73090
OREF 51:13199i,13200a
TI Pharmacology of carbutamide
AU Root, Mary A.
CS Lilly Research Labs., Indianapolis, IN
SO J. Pharmacol. Exptl. Therap. (1957), 119, 468-78
DT Journal
LA Unavailable

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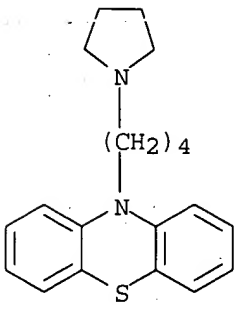
L4 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2003:118638 CAPLUS
DN 138:153540
TI Preparation of aminobutylphenothiazines, -iminodibenzyls, and related compounds as chemosensitizing agents against chloroquine resistant plasmodium falciparum
IN Lin, Ai J.; Guan, Jian; Kyle, Dennis E.; Milhous, Wilbur K.
PA USA
SO U.S. Pat. Appl. Publ., 27 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

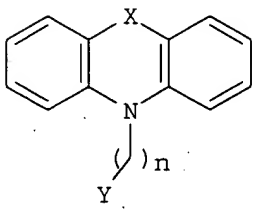
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003032801	A1	20030213	US 2001-849400	20010507
				US 2001-849400	20010507

OS MARPAT 138:153540
IT **443309-35-1P**, 10-(4-Pyrrolidin-1-ylbutyl)phenothiazine
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compd.; prepn. of aminobutylphenothiazines, -iminodibenzyls, and related compds. as chemosensitizing agents against chloroquine resistant plasmodium falciparum)
RN 443309-35-1 CAPLUS

CN 10H-Phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]- (9CI) (CA INDEX NAME)



GI



I

AB Title compds. [I; X = (substituted) alkyl, heteroatom; n = 4-6; Y = (substituted) alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, NR1R2; R1, R2 = H, heteroatom, (substituted) alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl; each ring structure may be substituted], were prepd. Thus, 10-(4-pyrrolidin-1-ylbutyl)phenothiazine (general prepn. given) at 50 ng/mL completely restored the sensitivity of TM91C235 cells to chloroquine.

L4 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2002:868744 CAPLUS
DN 137:370096
TI Tricyclic N-(aminoalkyl)-substituted phenothiazines, iminodibenzyls, iminostilbenes, and diphenylamines, active as chemosensitizing agents against chloroquine-resistant Plasmodium falciparum, and methods of making and using thereof
IN Lin, Ai J.; Guan, Jian; Kyle, Dennis E.; Milhous, Wilbur K.
PA United States Army Medical Research and Material Command, USA
SO PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002089810	A1	20021114	WO 2001-US14574	20010507

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,

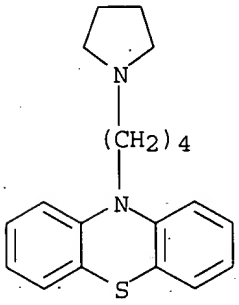
RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
WO 2001-US14574 20010507

OS MARPAT 137:370096

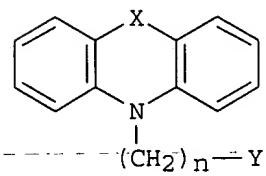
IT **443309-35-1P**, 10-[4-(Pyrrolidin-1-yl)butyl]phenothiazine
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; prepn. of phenothiazines, iminodibenzyls, iminostilbenes, and diphenylamines as antimalarial sensitizing agents for treatment of multidrug-resistant malaria with chloroquine and mefloquine)

RN 443309-35-1 CAPLUS

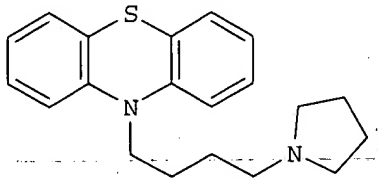
CN 10H-Phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]- (9CI) (CA INDEX NAME)



GI



I



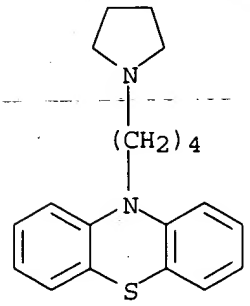
II

AB Title compds. I and pharmaceutically acceptable salts or prodrugs thereof are disclosed [wherein: X is a substituted or unsubstituted alkyl, a heteroatom, or 2 H atoms; n is 4, 5, or 6; Y is a substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or NR1R2; wherein R1 and R2 are each independently, H, a heteroatom, substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and wherein each ring structure is independently substituted or unsubstituted]. Also disclosed are chemosensitizing agents and methods of modulating, attenuating, reversing, or affecting a cell's or organism's resistance to a given drug such as an antimalarial. In particular, a group of compds. I were prepd. and shown to have improved anti-MDR (multidrug resistance) efficacy and reduced side effects (no data) in restoration of the clin. efficacy of antimalarials including mefloquine

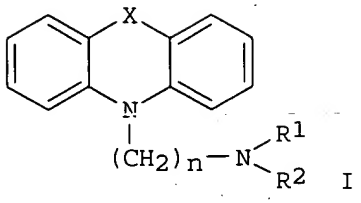
and chloroquine. Four of the compds. also showed moderate intrinsic antimalarial activity in the absence of chloroquine or mefloquine. Structure-activity relationships, e.g., regarding alkyl chain length, ring rigidity, and amino terminal size, are discussed. For instance, 4-chloro-1-butanol was converted to the THP ether (99%) and then used to N-alkylate phenothiazine (46%), followed by deprotection (100%), conversion of the resultant alc. to a chloride with SOCl2 (62%), and amination of the chloride (34%) to give the pyrrolidine deriv. II. At 50 ng/mL in vitro, II completely restored the sensitivity of TM91C235 cells [a highly drug-resistant malaria isolate from Thailand] to chloroquine, giving 99% cell growth suppression/inhibition. When tested on a different clone of Plasmodium falciparum, II gave superior MDR-reversing activity, with a fractional inhibitory concn. (FIC) of 0.21, using a 1:1 combination of chloroquine and II.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

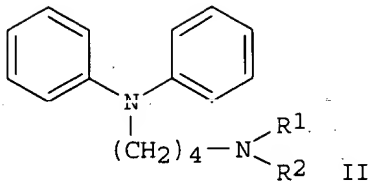
L4 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2002:372411 CAPLUS
DN 137:109247
TI Design, Synthesis, and Evaluation of New Chemosensitizers in Multi-Drug-Resistant Plasmodium falciparum
AU Guan, Jian; Kyle, Dennis E.; Gerena, Lucia; Zhang, Quan; Milhous, Wilbur K.; Lin, Ai J.
CS Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Silver Spring, MD, 20910, USA
SO Journal of Medicinal Chemistry (2002), 45(13), 2741-2748
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 137:109247
IT **443309-35-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of antimalarial drug chemosensitizing aminoalkyl phenothiazines, benzazepines, and diphenylamines)
RN 443309-35-1 CAPLUS
CN 10H-Phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]- (9CI) (CA INDEX NAME)



GI



I



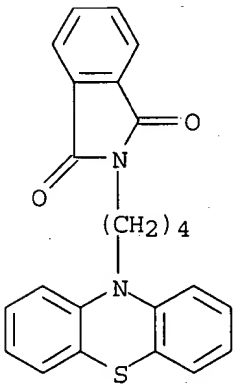
II

AB A series of new chemosensitizers (modulators) against chloroquine-resistant Plasmodium falciparum were designed and synthesized in an attempt to prep. modulators with enhancing drug-resistant reversing efficacy and minimal side effects. Phenothiazine, iminodibenzyl, and iminostilbene arom. amine ring systems I (X = S, CH2CH2, CH:CH; n = 4-6; R1, R2 = Me, Et, PhCH2; R1R2N = pyrrolinyl) and diphenylamines II (R1 = R2 = Et, R1R2N = pyrrolinyl) were examd. Various tertiary amino groups including either noncyclic or cyclic aliph. amines were introduced to explore the steric tolerance at the end of the side chain. The new compds. showed better drug-resistant reversing activity in chloroquine-resistant than in mefloquine-resistant cell lines and were generally more effective against chloroquine-resistant P. falciparum isolates from Southeast Asian (W2 and TM91C235) than those from South America (PC49 and RCS). Structure-activity relationship studies revealed that elongation of the alkyl side chain of the mol. retained the chemosensitizing activity, and analogs with four-carbon side chains showed superior activity. Furthermore, new modulators with phenothiazine ring exhibited the best chemosensitizing activity among the four different ring systems examd. Terminal amino function has limited steric tolerance as evidenced by the dramatic lose of the modulating activity, when the size of substituent at the amino group increases. The fractional inhibitory concn. (FIC) index of the best new modulator I (X = S, n = 4, R1R2N = pyrrolinyl) is 0.21, which is superior to that of verapamil (0.51), one of the best-known multi-drug-resistant reversing agents. Some of the analogs displayed moderate intrinsic in vitro antimalarial activity against a W-2 clone of P. falciparum.

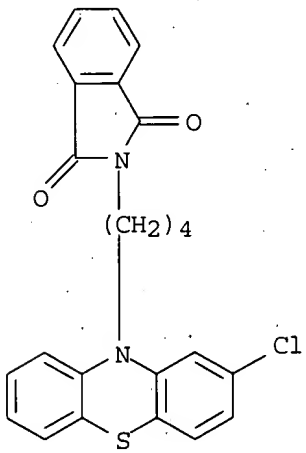
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2000:4293 CAPLUS
DN 132:273829
TI Relationship between cytotoxic activity and dipole moment for phthalimido- and chloroethyl-phenothiazines
AU Kurihara, Teruo; Motohashi, Noboru; Sakagami, Hiroshi; Molnar, Joseph
CS Faculty of Science, Josai University, Saitama, 350-0295, Japan
SO Anticancer Research (1999), 19(5B), 4081-4083
CODEN: ANTRD4; ISSN: 0250-7005
PB International Institute of Anticancer Research
DT Journal
LA English
IT **180388-70-9 180388-72-1 180388-74-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(relationship between cytotoxic activity and dipole moment for phthalimido- and chloroethyl-phenothiazines)
RN 180388-70-9 CAPLUS

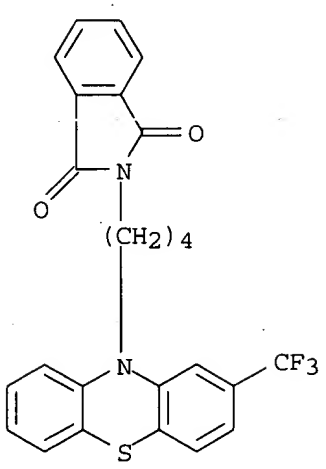
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



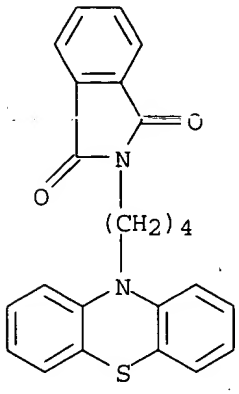
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



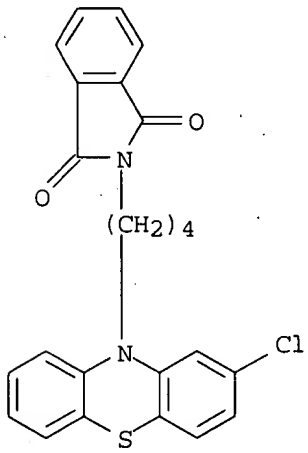
AB Among twelve phenothiazine-related compds., the cytotoxic activity of six "half-mustard type" phenothiazines was significantly higher than that of six phthalimido compds. 1-(2-Chloroethyl)-3-(2-chloro-10H-phenothiazin-10-yl)propylurea, 1-(2-chloroethyl)-3-(2-chloro-10H-phenothiazin-10-yl)butylurea and 1-(2-chloroethyl)-3-(2-trifluoromethyl-10H-phenothiazin-10-yl)butylurea showed the highest cytotoxic activity, in parallel with high .DELTA..mu. (difference between two dipole moments, .mu.g and .mu.e). There was also pos. relation between cytotoxic activity and MO energy such as .pi.-LUMO, .pi.-HOMO, and lone pair orbitals originated from O, N1, and N3 atoms. The present study demonstrated that cytotoxic activity of "half-mustard type" phenothiazines can be predicted by their dipole moments and MO energies.

RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

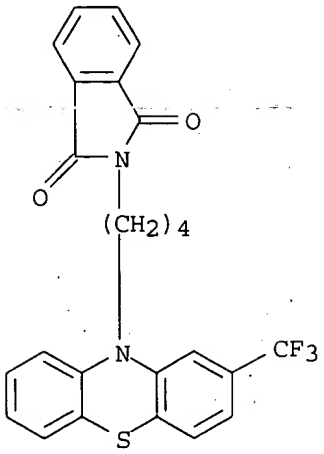
L4 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1999:654667 CAPLUS
DN 132:131770
TI Chemical structure and tumor type specificity of "half-mustard type" phenothiazines
AU Motohashi, Noboru; Kurihara, Teruo; Sakagami, Hiroshi; Szabo, Diana; Csuri, Klara; Molnar, Joseph
CS Department of Medicinal Chemistry, Meiji Pharmaceutical University, Tokyo, 204-8588, Japan
SO Anticancer Research (1999), 19(3A), 1859-1864
CODEN: ANTRD4; ISSN: 0250-7005
PB International Institute of Anticancer Research
DT Journal
LA English
IT **180388-70-9 180388-72-1 180388-74-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chem. structure-activity and tumor-type specificity of half-mustard type phenothiazines)
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



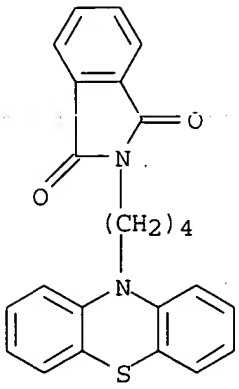
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



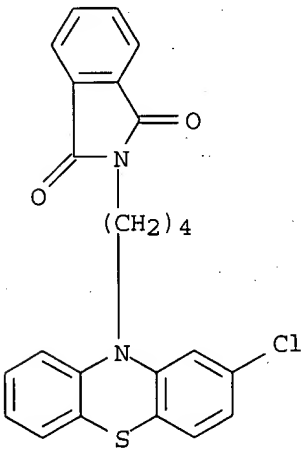
AB The antiproliferative activity of six half-mustard type phenothiazines against a total of 54 tumor cell lines: 4 leukemia, 9 non-small-cell lung, 7 colon-, 5 CNS-, 8 melanoma, 6 ovarian-, 8 renal-, 1 prostate and 6 breast cancer was detd. by NCI-Information Intensive-Approach. The C-2 position of phenothiazines were substituted with H, Cl and CF3 groups. The half-mustard and ring system was linked either by a propylene or a butylene bridge. Colon-cancer cell showed the highest sensitivity against half-mustard type phenothiazines, followed by leukemia, melanoma, prostate-, CNS-, breast-, lung-, renal and ovarian cancer cells. These data suggest the cancer-type-specific antitumor action of half-mustard type phenothiazines.

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

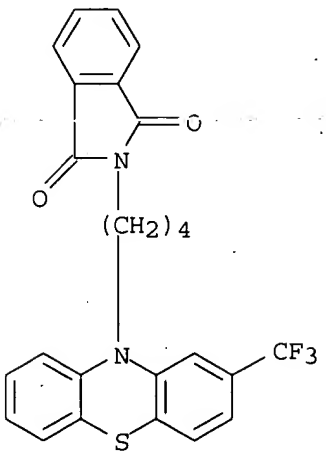
L4 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:282099 CAPLUS
DN 129:75984
TI The primary in vitro anticancer activity of "half-mustard type" phenothiazines in NCI's revised anticancer screening paradigm
AU Wuonola, Mark A.; Palfreyman, Michael G.; Motohashi, Noboru; Kawase, Masami; Gabay, Sabit; Gupta, Radha Raman; Molnar, Joseph
CS Scriptgen Pharmaceuticals, Inc., Medford, MA, 02155, USA
SO Anticancer Research (1998), 18(1A), 337-348
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **180388-70-9 180388-72-1 180388-74-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(primary in vitro anticancer activity of "half-mustard type" phenothiazines in NCI's revised anticancer screening paradigm)
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



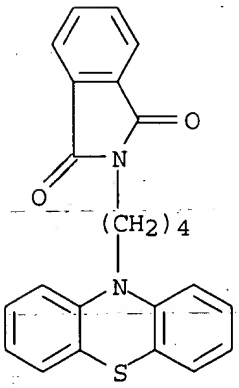
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



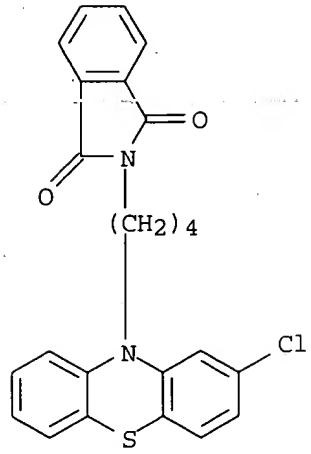
AB Some new phenothiazines have been synthesized on the basis of previous studies. The anticancer activity of "half-mustard type" phenothiazines was investigated on sixty different cancer cell lines in vitro. The percentage of growth (PG), 50% inhibition of growth (GI50), the tumor growth inhibition (TGI) and the concn. required for 50% lethality of cells (IC50) were examd. and calcd. in the presence of various (from 10-4 to 10-8 M) concns. of phenothiazine alkylurea derivs. The following cell lines were involved in the study: 6 leukemia, 9 non-small-cell lung cancer, 7 colon cancer, 6 central nervous system cancer, 8 melanoma, 6 ovarian cancer, 8 renal cancer, 2 prostate and 8 breast cancer cell lines. The anti-leukemic activity of four chloroethyl-substituted phenothiazine-alkylureas was shown by considerable growth inhibition, in the 10-5 M range, of the six different leukemia cell lines. The 50% inhibition of growth was nearly the same for the four compds. on all cell lines. Tumor growth inhibition (TGI) and IC50 value to cells varied from -4.0 to -4.66. The two derivs. with the butylene bridge were more effective than propylene linked compds. against the CCRP-CEM, HL60 (TB), K-562 and MOLT-4 cell lines. However, the anti-leukemic activity of the derivs. was nearly the same for RPMT 8226 and SR cell lines. The substituent at the 2- position of phenothiazine ring and the length of the linker between the side chain nitrogen and the phenothiazine ring system are apparently important for antileukemic activity. Four of the 9 non-small-cell lung cancer cell lines were sensitive, while the other 5 cell lines were not. The compds. had a slight growth inhibitory effect on colon cell carcinoma and melanoma cells in which case the butylene linker seemed to be more effective than the propylene linker. At the same time, all of the compds. were weak or mostly inactive on cancer cells from the central nervous system. One ovarian cancer line of the 6, the IGROVI was sensitive to butylurea phenothiazines, however, the other five were not sensitive at all. The difference in the sensitivity of various renal cell carcinomas was significant: 5 lines were not sensitive, three of them (786-0, RXF-393 and TK-10) were sensitive to only butylene-substituted phenothiazine-ureas, propylene substitution resulted in ineffective compds. The compds. were not able to inhibit the 2 prostate and 4 breast cancer cell lines, even at 10-4 M. It was interesting that propylene-linked ureas were more effective than butylene-linked derivs. on MCF-7, but butylene-linked derivs. were more effective than propylene-linked compds. on MDA MB-231 and MDA-N. In addn., MDA MB 435 was more sensitive to the trifluoromethyl derivs. than the compds. without this substituent. Since the phthalimido-alkyl phenothiazines were not

active at the first level of prescreen, these compds. were omitted from this study. The drug sensitivity of some cancer cell lines was not uniform for the different groups, therefore we postulate that the resistance can be related to some kind of (existing) drug-efflux mechanism. Apparently, the tumor specificity of phenothiazine alkylureas is more related to the leukemia specificity of alkylureas than to any CNS or lung specificity of phenothiazines.

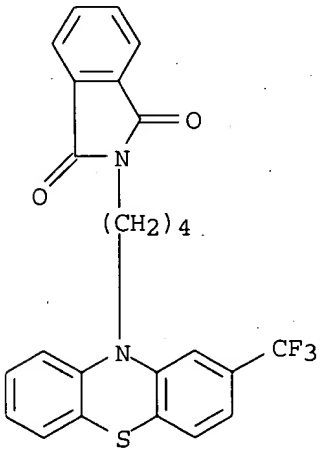
L4 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:200671 CAPLUS
DN 128:265747
TI Correlation between structure and diverse biological activities of "half-mustard type" phenothiazines
AU Motohashi, Noboru; Kurihara, Teruo; Satoh, Kazue; Sakagami, Hiroshi; Molnar, Joseph
CS Department of Medicinal Chemistry, Meiji College of Pharmacy, Tokyo, 188, Japan
SO Anticancer Research (1997), 17(6D), 4403-4406
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **180388-70-9 180388-72-1 180388-74-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(correlation between structure and diverse biol. activities of half-mustard type phenothiazines in relation to dipole moments and radical generation)
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



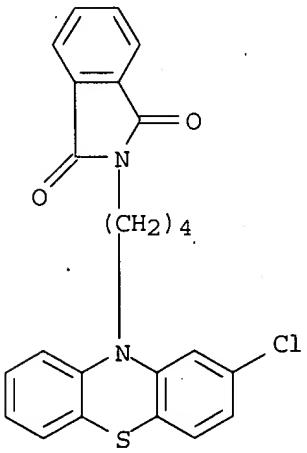
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



AB The structure and activity relation of fifteen "half-mustard type" phenothiazines and related compds. were investigated. These compds. did not show any direct bactericidal activity, possibly due to the lack of radical generation activity. Pretreatment with phenothiazines significantly reduced the lethality of Escherichia coli GN2411 infection, possibly due to activation of the host defense mechanism. Higher concns. of these compds. showed cytotoxic activity against several cultured tumor cell lines. However, no clear-cut relation was established between biol. activity and two dipole moments (.mu.g, .mu.e).

L4 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:49717 CAPLUS
DN 128:162543
TI Drug resistance reversal, antimutagenicity and antiretroviral effect of phthalimido- and chloroethyl-phenothiazines
AU Motohashi, Noboru; Kurihara, Teruo; Kawase, Masami; Hever, Aniko; Tanaka, Masaru; Szabo, Diana; Nacsa, Janos; Yamanaka, Wataru; Kerim, Ablikim;

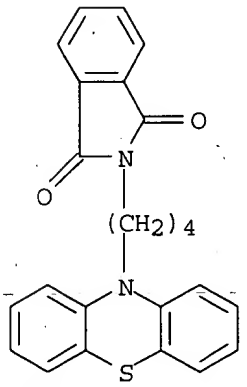
Molnar, Joseph
CS Department of Medicinal Chemistry, Meiji College of Pharmacy, Tanashi, 188, Japan
SO Anticancer Research (1997), 17(5A), 3537-3543
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **180388-72-1**, 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]-
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(drug resistance reversal, antimutagenicity and antiretroviral effect of phthalimido- and chloroethyl-phenothiazines)
RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



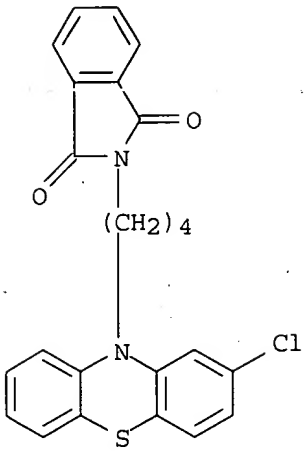
AB The effect of substituted phenothiazines was studied in three different systems; bacteria and cancer cells and reverse transcriptase enzyme of Moloney leukemia virus. F'lac and hemolysin plasmids were eliminated by some substituted phenothiazines from E. coli at a very low frequency. The same phenothiazine derivs. also were synergistic with tetracycline in bacteria and shown antimutagenic effect in Ames test. No mutagenic effects were obsd. in TA 98 strain of Salmonella typhimunium. Chloroethyl-substituted phenothiazines showed antimutagenicity equiv. to the parent compds.; however, phthalimido-substituted phenothiazines had higher antimutagenicity of 50%. P-glycoprotein responsible for multidrug resistance was also inhibited in tumor cells. The accumulation of the fluorescent rhodamine 123 in the phenothiazine treated multidrug resistant tumor cells was measured by flow cytometry. Some of the substituted phenothiazines were effective P-glycoprotein blockers, while some compds. had moderate activity, but others were without effect as compared to 5 .mu.M verapamil. On the basis of computer anal. there are some correlations between the biol. activities and the dipole moments, and entropy of the studied mols. Our results suggest that the inhibition of Hly+ plasmid replication and P-glycoprotein function may depend partly on similar electronic properties of the studied phenothiazine derivs. The

activity of Moloney leukemia virus reverse transcriptase was inhibited by the substituted phenothiazines, however, no basic differences were found in the activities of phthalimido- and chloroethyl substituted phenothiazines.

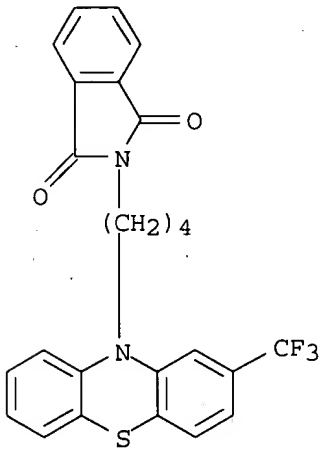
L4 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:49699 CAPLUS
DN 128:175800
TI The in vitro antitumor assay of "half-mustard type" phenothiazines in screens of AIDS-related leukemia and lymphomas
AU Wuonola, Mark A.; Palfreyman, Michael G.; Motohashi, Noboru; Kawase, Masami; Gabay, Sabit; Molnar, Joseph
CS SCRIPTGEN Pharmaceuticals, Inc., Medford, MA, 02155, USA
SO Anticancer Research (1997), 17(5A), 3425-3429
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **180388-70-9**, D 681648 **180388-72-1**, D 681650
180388-74-3, D 681652
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro antitumor assay of half-mustard type phenothiazines in screens of AIDS-related leukemia and lymphomas in relation to structure)
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



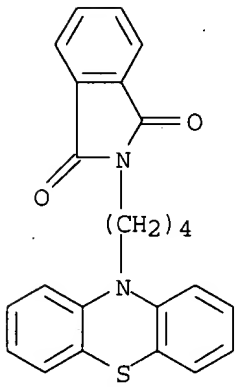
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



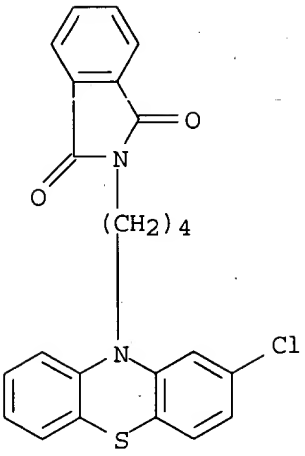
AB Twelve different "half-mustard type" phenothiazines were newly synthesized and tested on seven AIDS-related lymphoma (ARL) tumor cell lines, one leukemia CCRF-CEM cell culture and five different lymphoma lines; RL, KD488, AS283, PA682 and SU-DHL-7 cell lines. The alkylene-urea substituted phenothiazines affected the growth and inhibited the growth rate of AIDS-related lymphoma cells. The Cl-substituent at the 2-position was more effective than the CF3 substitution. In AIDS-related leukemia, also the compds. with Cl at the 2-position with propylene or butylene linkers, -(CH2)3- and -(CH2)4-, resp., were more effective than the CF3 substituted compds. Two of the six phenothiazine-substituted alkyl-urea derivs., i.e., 1-(2-chloroethyl)-3-(2-chloro-10H-phenothiazin-10-yl)propyl-1-urea (GI50=-5.66, TGI=-5.04) and 1-(2-chloroethyl)-3-(2-chloro-10H-phenothiazin-10-yl)butyl-1-urea (GI50=-5.61, TGI=-5.12) exhibited antitumor activity for AIDS-related leukemia and five AIDS-related lymphomas. The trifluoromethyl-substituted derivs. were not as effective on AIDS-related tumor cell lines. Apparently, the substituent at the 2-position on the phenothiazine and the alkylene no. of the linker

attached to the nitrogen of the phenothiazine ring have an important role in the compd.'s antitumor effects on AIDS-related leukemia and lymphomas.

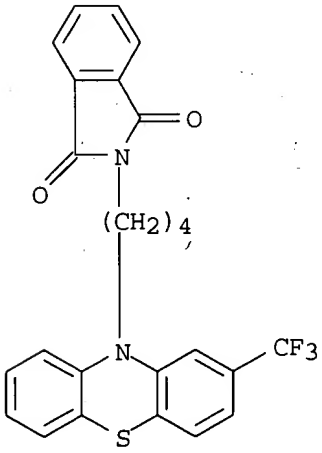
L4 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:49698 CAPLUS
DN 128:162631
TI The primary in vitro antitumor screening of "half-mustard type" phenothiazines
AU Wuonola, Mark A.; Palfreyman, Michael G.; Motohashi, Noboru; Kawase, Masami; Gabay, Sabit; Nacsa, Janos; Molnar, Joseph
CS SCRIPTGEN Pharmaceuticals, Inc., Medford, MA, 02155, USA
SO Anticancer Research (1997), 17(5A), 3409-3423
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **180388-70-9**, D 681648 **180388-72-1**, D 681650
180388-74-3, D 681652
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(the primary in vitro antitumor screening of "half-mustard type" phenothiazines)
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



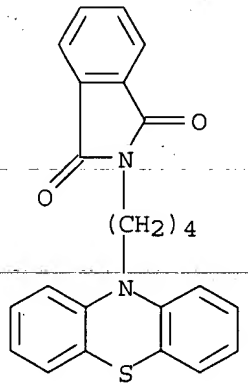
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



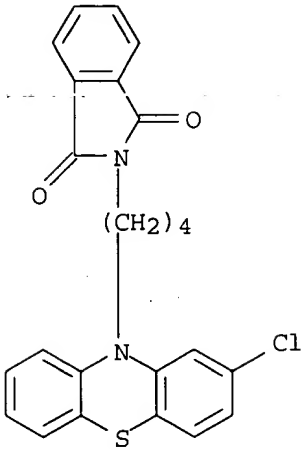
AB The antitumor effects of "half-mustard type" phenothiazines were studied on 57 different tumor cell lines, including leukemias, non-small lung cancer, colon, central nervous system, ovarian, renal, breast, and prostate cancer, as well as melanoma cell cultures. Alkyl-urea derivs. of phenothiazines displayed in vitro antitumor activity. The phenothiazine phthalimido derivs. (1-6) were not active on the majority of cancer cell cultures. In contrast, propylureas (9, 11) were active against some leukemia cell types. Only two compds. with the butylene [(CH2)4] linker (10, 12) were active against non-small lung cancer cells. Compds. contg. the propylene linker were less effective. On colon cancer lines, tumor cells from the central nervous system and on melanoma cells the same compds. were effective, however, having substituents at the 2-position of phenothiazine seems to be important. Surprisingly, the majority of ovarian cancer cell lines (except one type, IGROVI) and five of eight renal cancer lines were not sensitive to these phenothiazine derivs. The two butylene linked phenothiazine ureas (10, 12) had moderate antiproliferative action on two renal cancer cell lines. The prostate

cancer and some breast cancer cell lines were not sensitive. Nevertheless some breast cancer cell lines were apparently sensitive to CF3-substituted phenothiazine alkylureas. On the basis of these expts. one may postulate that in the case of insensitive cells an mdr-gene encoded multidrug resistance efflux pump is responsible for the resistance. The selectivity or organ cell specificity of the effective phenothiazines will be targeted for improvement in further studies, in order to avoid the general cytotoxic effects of "half mustard type" phenothiazines.

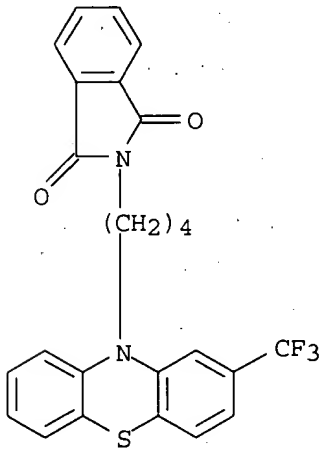
L4 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1996:703922 CAPLUS
DN 126:26380
TI Synthesis and antitumor activity of 1-[2-(chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl]-1-ureas as potent anticancer agents
AU Motohashi, Noboru; Kawase, Masami; Kurihara, Teruo; Hever, Aniko; Nagy, Szilvia; Ocsocvszki, Imre; Tanaka, Masaru; Molnar, Joseph
CS Department Medicinal Chemistry, Meiji College Pharmacy, Tanashi, 188, Japan
SO Anticancer Research (1996), 16(5A), 2525-2532
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **180388-70-9P 180388-72-1P 180388-74-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(synthesis and antitumor activity of [(chloroethyl)(substituted-phenothiazinyl)alkyl]ureas in relation to structure)
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



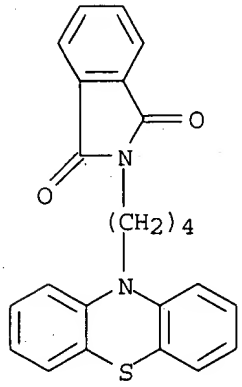
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



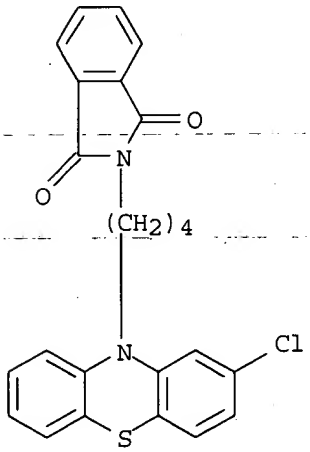
AB 10-[N-(Phthalimido)alkyl]-2-substituted-10H-phenothiazines and 1-(2-chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas were synthesized and found to have antiproliferative effects on human HEp-2 and L5178Y cell cultures. The multi-drug resistant subline of mouse lymphoma was sensitive to the reversal effects of some 10-[N-(phthalimido)alkyl]-2-substituted-10H-phenothiazines, while 1-(2-chloro-ethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas were less effective but had a similar degree of antiproliferative effect on both cell lines.

L4 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1996:518725 CAPLUS
DN 125:211824
TI Antitumor activity of phenothiazine-related compounds
AU Nagy, Sylvia; Argyelan, George; Molnar, Joseph; Kawase, Masami; Motohashi, Noboru
CS Faculty Medicine, Albert Szent-Gyorgyi Medical University, Szeged, H-6720,

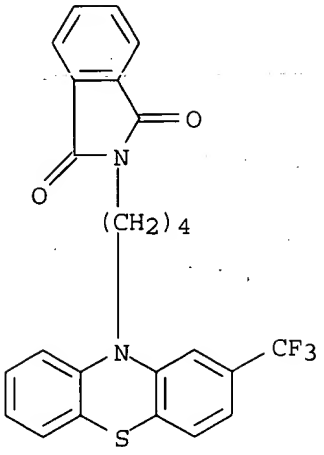
Hung.
SO Anticancer Research (1996), 16(4A), 1915-1918
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **180388-70-9 180388-72-1 180388-74-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phenothiazine deriv. antitumor activity)
RN 180388-70-9 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-72-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



AB One of the biggest challenges in health care is the fight against tumors. Some phenothiazines have antitumor activity on HEp-2 tumor cells. In this study, we tested the antitumor effects of three series such as 10-nonsubstituted phenothiazines, 10-[n-(phthalimido)alkyl]-2-substituted-10H-phenothiazines and 1-(chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas with H, Cl and CF3 substitution at position C2. The TCID50 of phenothiazines was affected by the H, Cl and CF3 at C2. The trifluoromethyl deriv. of phenothiazine showed potent (R = CF3, TCID50 = 4.7 .mu.g) activity, whereas the chlorine deriv. of phenothiazine (R = Cl, TCID50 = 62.5 .mu.g) had a relatively weak effect. In the group of 10-[n-(phthalimido)alkyl]-2-substituted-10H-phenothiazines, 10-[3-(phthalimido)propyl]-10H-phenothiazine (R = H, n = 3, TCID50 = 11.5 .mu.g), 10-[4-(phthalimido)butyl]-10H-phenothiazine (R = H, n = 4, TCID50 = 7.8 .mu.g) and 10-[3-(phthalimido)propyl]-2-trifluoromethyl-10H-phenothiazine (R = CF3, n = 3, TCID50 = 11.5 .mu.g) were very effective. On the other hand, TCID50 of 10-[3-(phthalimido)propyl]-2-chloro-10H-phenothiazine (R = Cl, n = 3, TCID50 = 75.0 .mu.g), 10-[4-(phthalimido)butyl]-2-chloro-10H-phenothiazine (R = Cl, n = 4, TCID50 = 31.3 .mu.g) and 10-[4-(phthalimido)butyl]-2-trifluoromethyl-10H-phenothiazine (R = CF3, n = 4, TCID50 = 50.0 .mu.g) were about 4-8 times less effective than 10-[4-(phthalimido)butyl]-10H-phenothiazine (R = H, n = 4, TCID50 = 7.8 .mu.g). Among six 1-(chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas, two chlorine compds. such as 1-(2-chloroethyl)-3-(2-chloro-10H-phenothiazin-10-yl)propyl-1-urea (R = Cl, n = 3, TCID50 = 6.3 .mu.g), 1-(2-chloroethyl)-3-(2-chloro-10H-phenothiazin-10-yl)butyl-1-urea (R = Cl, n = 4, TCID50 = 7.8 .mu.g), and 1-(2-chloroethyl)-3-(2-trifluoromethyl-10H-phenothiazin-10-yl)butyl-1-urea (R = CF3, n = 4, TCID50 = 7.8 .mu.g) were significantly active. Tests showed that the substitution at 2C position apparently affected the anti-HEp-2 tumor cell activity; that the length of the aliph. side chain at 10N contributes to the anti-tumor activity; and that the TCID50 values of the derivs. with a butylene group (-C4H8-) were lower than those with propylene group (-C3H6-) except 10-[4-(phthalimido)butyl]-2-trifuoromethyl-10H-phenothiazine and 1-(2-chloroethyl)-3-(2-chloro-10H-phenothiazin-10yl) butyl-1-urea.

L4 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1996:472497 CAPLUS
DN 125:211925

TI Immunomodulating activities on cellular cytotoxicity and the blast transformation of human lymphocytes by 10-n-(phthalimido) alkyl-2-substituted-10H-phenothiazines and 1-(2-chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas

AU Petri, Ilidiko B.; Szekeres, Eva; Varga, Eva; Berek, Imre; Mólnar, Joseph; Berek, Livia; Kawase, Masami; Motohashi, Noboru

CS Blood Transfusion Centre, Albert Szent-Gyorgyi Medical University, Szeged, H-6720, Hung.

SO Anticancer Research (1996), 16(3A), 1247-1250
CODEN: ANTRD4; ISSN: 0250-7005

PB Anticancer Research

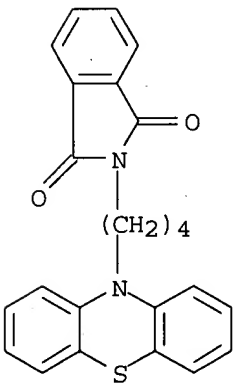
DT Journal

LA English

IT **180388-70-9 180388-72-1 180388-74-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunomodulating activities on cellular cytotoxicity and blast transformation of human lymphocytes by)

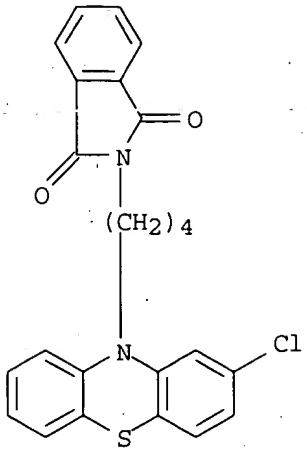
RN 180388-70-9 CAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)

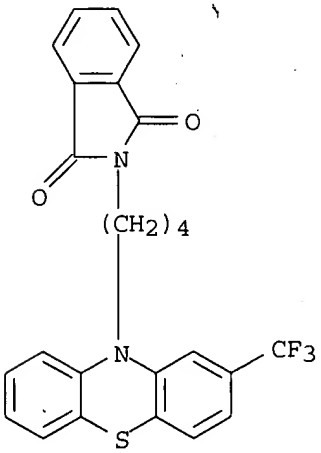


RN 180388-72-1 CAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



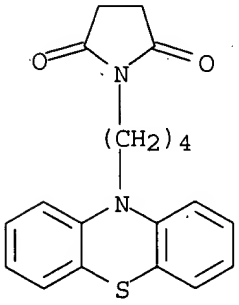
RN 180388-74-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)



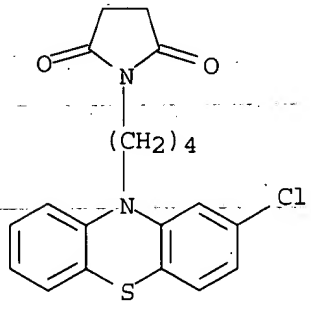
AB Phenothiazines, 10-n-(phthalimido)alkyl-2-substituted-10H-phenothiazines, and 1-(2-chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas were investigated for their effects on antibody-dependent cellular cytotoxicity (ADCC), natural killer (NK) cells and the blast transformation of human peripheral blood mononuclear cells. All of the compds. dose-dependently suppressed mitogen stimulated T cell proliferation. In contrast, a strong enhancing effect on NK cell activity was detected mostly in the case of 1-(2-chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-10-ureas and their related compds. The stimulating effect directly influenced the NK cells and was demonstrated at all tested concns.

L4 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1996:239126 CAPLUS
DN 124:332043
TI Induction of DNA fragmentation in human myelogenous leukemic cell lines by phenothiazine-related compounds

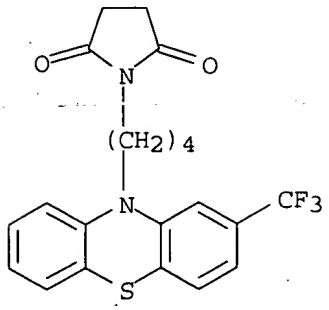
AU Sakagami, Kiroshi; Takahashi, Hideo; Yoshida, Hiroshi; Yamamura, Mitsuhisa; Fukuchi, Kunihiko; Gomi, Kunihide; Motohashi, Noboru; Takeda, Minoru
CS School Medicine, Showa University, Tokyo, 142, Japan
SO Anticancer Research (1995), 15(6B), 2533-40
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
IT **176657-40-2 176657-42-4 176657-44-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(induction of DNA fragmentation in human myelogenous leukemic cell lines by phenothiazine-related compds.)
RN 176657-40-2 CAPLUS
CN 2,5-Pyrrolidinedione, 1-[4-(10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 176657-42-4 CAPLUS
CN 2,5-Pyrrolidinedione, 1-[4-(2-chloro-10H-phenothiazin-10-yl)butyl]- (9CI) (CA INDEX NAME)



RN 176657-44-6 CAPLUS
CN 2,5-Pyrrolidinedione, 1-[4-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]butyl]- (9CI) (CA INDEX NAME)

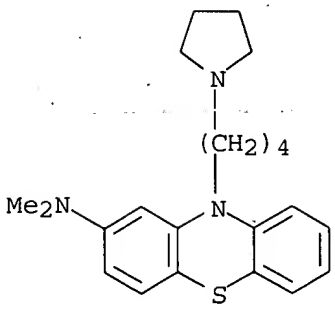


AB A series of phenothiazine, benzo[a]phenothiazine and benz[c]acridine derivs. were compared for their ability to induce nucleosome-sized DNA fragmentation (a biochem. hallmark of apoptosis), using agarose gel electrophoresis and a fluorescence activated cell sorter. Significant DNA fragmentation-inducing activity was detected in 12H-benzo[a]phenothiazine, 5-oxo-5H-benzo[a]phenothiazine and 9-methyl-12H-benzo[a]phenothiazine, which induced the monocytic differentiation of human myelogenous leukemic cell lines. On the other hand, an other three benzo[a]phenothiazines, six 10-[n-(phthalimido)alkyl]2-substituted-10H-phenothiazines, six 1-(2-chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl-1-ureas, and twelve benz[c]acridines showed little or no DNA fragmentation-inducing activity. Active benzo[a]phenothiazines induced DNA fragmentation in four human myelogenous leukemic cell lines (HL-60, ML-1, U-937, THP-1), but not in human T-cell leukemic MOLT-4 and erythroleukemic K-562 cell lines, which were also resistant to other apoptosis-inducing agents. Ca2+-depletion from the culture medium did not significantly affect their DNA fragmentation-inducing activity. The differentiation and apoptosis-inducing activity of benzo[a]phenothiazines have an important role for their medicinal efficacy.

L4 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1962:483298 CAPLUS
DN 57:83298
OREF 57:16630g-i,16631a-d
TI Dimethylaminophenothiazines
IN Craig, Paul N.
PA Smith Kline & French Laboratories
SO 4 pp.
DT Patent
LA Unavailable

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 3047572		19620731	US	19581210

IT **95138-82-2**, Phenothiazine, 2-(dimethylamino)-10-[4-(1-pyrrolidinyl)butyl]-
(prepn. of)
RN 95138-82-2 CAPLUS
CN Phenothiazine, 2-(dimethylamino)-10-[4-(1-pyrrolidinyl)butyl]- (7CI) (CA INDEX NAME)



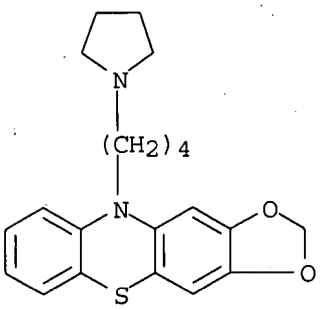
AB The title compds. were prepd. and found useful as tranquilizers, calmatives, antiemetics, and general central nervous system depressants. 4-Bromo-3-nitrodimethylaniline (84 g.) in 600 ml. alc. treated with an aq. alc. soln. of Na o-bromothiophenol, the mixt. refluxed 20 hrs., and the product crystd. gave 2'bromo-2-nitro-4-dimethylaminodiphenyl sulfide (I), m. 120-1.degree. (alc.). I (91.9 g.) in 690 ml. concd. HCl treated with 235 g. SnCl2, refluxed 4 hrs., made alk., and the mixt. extd. with hot C6H6 gave 2'-bromo-2-amino-4-dimethylaminodiphenyl sulfide (II), m. 126-7.degree.. II (49.5 g.), 28.8 g. anhyd. K2CO3, 8 g. CuI, and 2.88 g. Cu bronze powder refluxed 500 ml. HCONMe2 gave 2-dimethylaminophenothiazine(III),m. 157-8.degree.; HBr salt was made. III(19.5 g.) in 700 ml. xylene treated 80 min. under reflux with 4 g. NaNH2, then refluxed 6 hrs. with 12.4 g. 3-chloro-1-dimethylaminopropane in 50 ml. xylene, extd. with AcOH, neutralized, and taken up in C6H6 gave 10-(3-dimethylaminopropyl)-2-dimethylaminophenothiazine, b0.3-0.5 215-20.degree.; di-HCl salt m. 214-15.degree.. III (24.2 g.) and 2.4 g. LiNH2 in 100 ml. PhMe refluxed 1 hr., then 7 hrs. under N with 16.3 g. 2-chloro-1-diethylaminopropane gave 10(diethylaminoisopropyl)-2-dimethylaminophenothiazine; a maleic acid salt was obtained. III (48.4 g.) and 8.3 g. NaNH2 in 500 ml. xylene refluxed 1.5 hrs. under N, then 5 hrs. with 41.8 g. 3-chloro-2-methyl-1-(N-methylpiperazinyl)propane gave 10-[2-methyl-1-(N-methylpiperazinyl)propyl]-2-dimethylaminophenothiazine; HBr salt was made. III (12.1 g.) in 500 ml. xylene and 1.2 g. LiNH2 refluxed 2 hrs., then 5 hrs. with 10.4 g. 1-formyl-4-(3-chloropropyl)piperazine in 100 ml. xylene gave 10-(3-N-formylpiperazinyl)propyl)-2-dimethylaminophenothiazine (IV) as an oil. IV (38.7 g.) in 200 ml. alc. and 125 ml. H20 contg. 30 ml. 40% NaOH refluxed 2 hrs. gave 10-(3'-piperazinylpropyl)-2-dimethylaminophenothiazine (V) as an oil. V (55.2 g.), 19.6 g. beta.-bromoethanol, and 21.6 g. K2CO3 in 700 ml. PhMe refluxed 6 hrs. gave 10-(3-(N-.beta.-hydroxyethylpiperazinyl)propyl)-2-dimethylaminophenothiazine (VI); acetate prepd. VI (20.6 g.) in 300 ml. C6H6 and 4 g. AcCl left 10 hrs. at room temp. and the oily base treated with ethereal HCl gave 10-[3-(.beta.-acetoxyethylpiperazinyl)propyl]-2-dimethylaminophenothiazine-HCl. V (18.4 g.), 8.8 g. 2-bromo-2'-hydroxyethyl ether, and 7.6 g. K2CO3 in 500 ml. xylene refluxed 15 hrs. gave 10-[3-(N-hydroxyethoxyethylpiperazinyl)propyl]-2-dimethylaminophenothiazine; tartrate salt prepd. III (60.5 g.) and 10.1 g. NaNH2 in 800 ml. xylene refluxed with gradual addn. of 55.6 g. 4-bromo-1-N-pyrrolidinylbutane gave 10-[4-(N-pyrrolidinylbutyl)]2-dimethylaminophenothiazine; bismethylenesalicylate salt prepd. V (11 g.) in 50 ml. HCONMe2 treated with 7.5 g. p-nitrophenethyl bromide in 10 ml. HCONMe2, stirred 6 hrs. at 95-105.degree., poured into 1600 ml. H2O, the mixt. made alk., extd. with CHCl3, washed, filtered, and evapd. gave 10-[3-(p-nitrophenethylpiperazinyl)propyl]-2-dimethylaminophenothiazine (VII). VII

(11.7 g.) in 300 ml. alc. and 0.3 g. PtO2 hydrogenated 1 hr. at 50 lb./sq. in. gave 10-[3-(p-aminophenethylpiperazinyl)propyl]-2-dimethylaminophenothiazine.

L4 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1961:8225 CAPLUS
DN 55:8225
OREF 55:1667a-c
TI Basic alkylthioalkyl esters of phenothiazine-10-carboxylic acid and their salts
IN Myers, Gorden S.; Davis, Martin A.
PA American Home Products Corp.
DT Patent
LA Unavailable
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2951077		19600830	US	

IT **112745-72-9**, 10H-1,3-Dioxolo[4,5-b]phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]-
(prepn. of)
RN 112745-72-9 CAPLUS
CN 10H-1,3-Dioxolo[4,5-b]phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]- (6CI) (CA INDEX NAME)



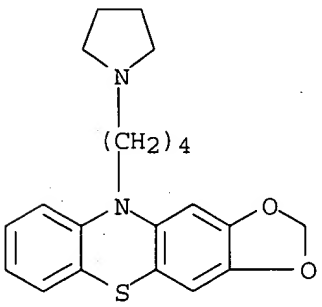
AB The title compds. were bacteriostatic agents. A soln. of .beta.-(diethylaminoethylthio)ethanol in 50 ml. pyridine was added to 26.1 g. phenothiazine-10-carboxylic acid chloride in 50 ml. dry pyridine. The mixt. was maintained at room temp. during addn. (20 min.), heated 30 min. at 25-90.degree., then for another 45 min. at 90.degree., cooled, and poured onto 400 ml. ice water. 2-(Diethylaminoethylthio)ethyl phenothiazine-10-carboxylate (I) was liberated from soln. by adding NaOH. I was extd. with ether, and washed with water repeatedly till free from pyridine. Evapn. of the solvent gave I as a dark oil. The citrate of I was prepd. by treating an ethereal soln. of I with an equal wt. of citric acid in acetone, m. 99-101.degree. (decompn.). Similarly were obtained: I.MeBr, m. 155-60.degree. (decompn.); 2-(dimethylaminoethylthio)ethyl phenothiazine-10-carboxylate maleate, m. 106-9.degree.; 2-(diisopropylaminoethylthio)ethyl phenothiazine-10-carboxylate citrate, m. 49-54.degree..

L4 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1961:8224 CAPLUS
DN 55:8224

OREF 55:1666f-i,1667a
TI Methylenedioxy-substituted phenothiazines
IN Gordon, Maxwell
PA Smith, Kline & French Laboratories
DT Patent
LA Unavailable
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2945031		19600712	US	

IT **112745-72-9**, 10H-1,3-Dioxolo[4,5-b]phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]-
(prepn. of)
RN 112745-72-9 CAPLUS
CN 10H-1,3-Dioxolo[4,5-b]phenothiazine, 10-[4-(1-pyrrolidinyl)butyl]- (6CI) (CA INDEX NAME)



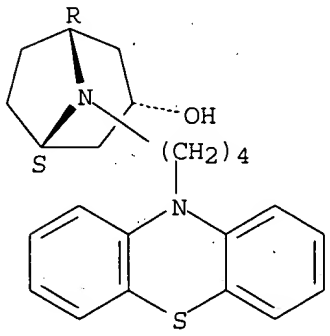
AB 6-Bromopiperonal (I) (m. 127-8.5.degree.) was prepd. from 300 g. piperonal and 120 ml. Br in 900 ml. HOAc. I (210 g.) was added in small portions to 1400 ml. concd. HNO3 while the temp. was kept at 25.degree. and the mixt. then decompd. with ice H2O to give 4-nitro-5-bromocatechol methylene ether (II), m. 88-9.degree.. A soln. of Na o-bromothiophenol (from 113.4 g. o-bromothiophenol, 500 ml. EtOH, 23.9 g. NaOH, and 25 ml. H2O) was added dropwise to 147.6 g. II in 1250 ml. hot EtOH, the mixt. refluxed 3 hrs., cooled, and filtered to give 4,5-methylenedioxy-2-nitro-2'-bromodiphenyl sulfide (III), m. 149-50.degree.. III (186 g.) was reduced with 426.6 g. SnCl2 and 675 ml. concd. HCl in 675 ml. EtOH to 2-amino-4,5-methylenedioxy-2'-bromodiphenyl sulfide (IV), m. 142-3.5.degree.. IV (3.6 g.), 1.56 g. anhyd. K2CO3, and 0.2 g. Cu powder in 45 ml. HCONMe2 was refluxed 6 hrs., filtered, and the filtrate dild. with H2O to ppt. 2,3-methylenedioxyphenothiazine (V), m. 202-3.5.degree.. V (24.3 g.) and 2.4 g. LiNH2 in 100 ml. dry toluene was refluxed 3 hrs., 13.3 g. 3-chloro-1-dimethylaminopropane in 10 ml. toluene added, the mixt. refluxed an addnl. 4 hrs., and from this mixt. an oil, 10-(3-dimethylaminopropyl)-2,3-methylenedioxyphenothiazine, isolated. 2,3-Methylenedioxyphenothiazines with the following substituents were also prepd.: 10-(diethylaminoisopropyl), 10-[2-methyl-1-(N-methylpiperazinyl)propyl], 10-[3-(N-formylpiperazinyl)propyl], 10-(3-piperazinylpropyl), 10-{3-[N-(.beta.-hydroxyethyl)piperazinyl]propyl}, 10-[3-(N-acetoxyethylpiperazinyl)propyl], 10-{3-[N-(hydroxyethoxyethyl)piperazinyl]propyl}, 10-(4-pyrrolidinylbutyl), 10-{3-[N-(p-nitrophenethyl)piperazinyl]propyl}, and 10-{3-[N-(p-aminophenethyl)piperazinyl]propyl}.

L4 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1958:104438 CAPLUS
DN 52:104438
OREF 52:18502d-i,18503a-b
TI N-[(10-Phenothiazinyl)-lower alkyl]-1,5-iminocycloalkanes
IN Zenitz, Bernard L.
PA Sterling Drug Inc.
DT Patent
LA Unavailable
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2838505		19580610	US	

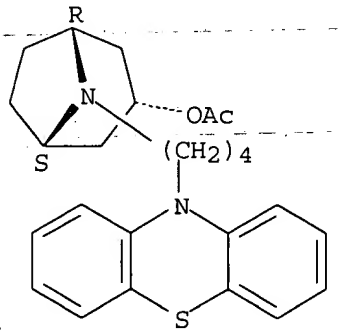
IT **119148-95-7**, Nortropine, 8-(4-phenothiazin-10-ylbutyl)-
123885-14-3, Nortropine, 8-(4-phenothiazin-10-ylbutyl)-, acetate (prepn. of)
RN 119148-95-7 CAPLUS
CN Nortropine, 8-(4-phenothiazin-10-ylbutyl)- (6CI) (CA INDEX NAME)

Relative stereochemistry.



RN 123885-14-3 CAPLUS
CN Nortropine, 8-(4-phenothiazin-10-ylbutyl)-, acetate (6CI) (CA INDEX NAME)

Relative stereochemistry.

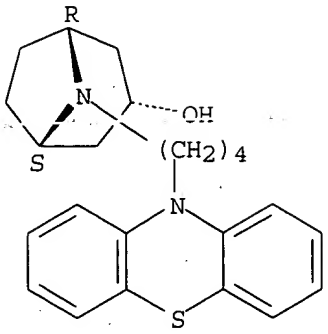


GI For diagram(s), see printed CA Issue.
AB Compds. (I) were prepd., where Y and Y' are the same or different H, halogen, lower-alkyl, or lower-alkoxy, A is a lower-alkylene group, n is 1 or 2, R is H, and R' is OH, O-Acyl, Cl, Br, or RR' is O. The I are useful

as hypotensive agents, antinauseants, antipyretics, and sedatives. (All m.ps. are cor.). 10-(3-Chloropropyl)phenothiazine (13.8 g.) and 7.1 g. tropine (II) in 25 cc. HCONMe2 heated 24 hrs. on a steam bath, cooled in an ice bath, dild. with 50 cc. anhyd. Et2O, again cooled, the ppt. filtered off, triturated with Me2CO, the ppt. filtered off, and recrystd. 1st from 600 cc. iso-PrOH and then twice from 50 cc. abs. EtOH-75 cc. anhyd. Et2O with C gave 8.0 g. 8-[3-(10-phenothiazinzyl)propyl]-3-hydroxynartropine-MeCl, m. 224.5-5.5 (decompn.). Similarly were prepd. the following I (R = H in all cases) (Y, Y', A, n, R', m.p. given): H, H, (CH2)2, 1, OH, - (methochloride, m. 221-3.degree.); H, H, (CH2)2, 1, OAc, - (methochloride, m. 241-3.degree.); H, H, (CH2)2, 1, OAc, - (methochloride, m. 232.5-3.5.degree.); H, H, (CH2)2, 1, OH, 126-8.degree. (HCl salt, m. 246.5-8.5.degree.) [prepd. by treating II with H2O2 to obtain II oxide (III), m. 228-9.degree., treating III with Ac2O to obtain N,O-diacetylnortropine, and sapong. to nortropine (IV), m. 161-3.degree. (Me2CO), and treating with 10-(2-bromoethyl)phenothiazine]; H, H, (CH2)2, 1, OAc, 114-15.degree.; H, H, (CH2)3, 1, OH, 87.5-9.0.degree. (HCl salt, m. 177-9.degree.); H, H, (CH2)3, 1, OAc, 141.0-3.5.degree. (HCl salt, m. 218-20.degree.); H, H, (CH2)3, 1, O2CCH:CHPh, 139.0-41.5.degree.; H, H, (CH2)3, 1, O2CC6H2(OMe)3-3,4,5, 151.5-3.5.degree.; H, H, (CH2)3, 1, OBz, 121-2.degree.; H, H, (CH2)4, 1, OH, 133-7.degree.; H, H, (CH2)4, 1, OAc, 115.5-18.0.degree.; H, H, (CH2)5, 1, OH, - (HCl salt, m. 192-4.degree.) [prepd. from p-MeC6H4SO3(CH2)5Cl, b0.14-0.23 148-53.degree., nD25 1.5157, by treating with phenothiazine to obtain 10-(5-chloropentyl)phenothiazine, b0.09 157.5-60.0.degree., nD25 1.6391, followed by treatment with IV]; 2-Cl, H, (CH2)3, 1, OH, 119.5-22.0.degree.; 2-Cl, H, (CH2)3, 1, O2CCH:CHPh, 130.5-1.5.degree.; 2-Cl, H, (CH2)3, 1, OBz, 94.0-8.5.degree.; 2-Cl, H, (CH2)3, 1, O2CC6H2(OMe)3-3,4,5, 155-8.degree.; 3-Cl, H, (CH2)3, 1, OH, 146,5-8.5.degree. [prepd. from p-MeC6H4SO3(CH2)3Cl, b0.04 141-7.degree., nD25 1.6660, and (3-chloropropyl)phenothiazine to obtain 3-chloro-10-(3-chloropropyl)phenothiazine, m. 45.0-7.5.degree., and treatment with IV]; 3-Cl, H, (CH2)3, 1, OAc, 107.5-9.5.degree.; 3-Cl, H, (CH2)3, 1, OBz, 102.0-4.5.degree.; 3-Cl, H, (CH2)3, 1, O2CCH:CHPh, 114.5-15.5.degree.; 3-Cl, H, (CH2)3, 1, O2CC6H2(OMe)3-3,4,5, 165.0-6.5.degree.; 2-Cl, H, (CH2)3, 1, OH, 96.5-101.degree. [prepd. from pseudonortropine (m. 132-4.degree.) and CO2 to obtain pseudonortropine carbamate, m. 141-2.degree., followed by treatment with 2-chloro-10-(3-chloropropyl)phenothiazine]. When n is 2 in I, the compds. are derivs. of granatanine.

L4 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1957:73091 CAPLUS
DN 51:73091
OREF 51:13200a-d
TI Structure activity relationships of some phenothiazine-substituted nortropane derivatives
AU Long, J. P.; Lands, A. M.; Zenitz, B. L.
CS Sterling-Winthrop Inst., Rensselaer, NY
SO J. Pharmacol. Exptl. Therap. (1957), 119, 479-84
DT Journal
LA Unavailable
IT **119148-95-7**, Nortropine, 8-(4-phenothiazin-10-ylbutyl)- (pharmacology of)
RN 119148-95-7 CAPLUS
CN Nortropine, 8-(4-phenothiazin-10-ylbutyl)- (6CI) (CA INDEX NAME)

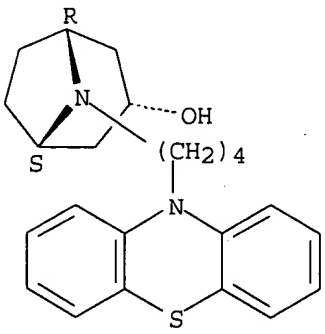
Relative stereochemistry.

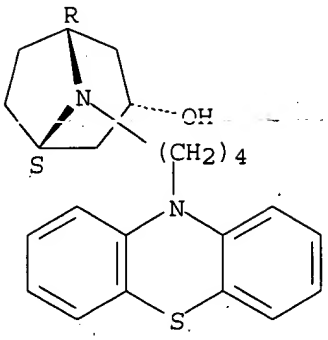


AB A series of 13 nortropane-substituted phenothiazine derivs. were investigated for central-nervous-system activity (production of hypothermia in mice) and peripheral adrenolytic action (reversal of adrenaline effects in dogs). The compds. had a di-, tri-, tetra-, or pentamethylene bridge joining the phenothiazine N with the tropane N and had H, OH, or a 3,4,5-trimethoxybenzoxy radical in the 3-position of the tropane ring. In most respects the adrenolytic activity closely paralleled the central-nervous-system activity. The trans isomers showed higher activity than the cis isomers or the 3-dehydroxy derivs. The exptl. data support the hypophysis that a drug-receptor interaction is involved both centrally and peripherally, and that these receptors are quite similar with respect to the compds. studied. 2-Chloro substitution in the phenothiazine ring increases the central-nervous-system activity without a consistent alteration of the peripheral adrenolytic activity.

L4 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1957:73090 CAPLUS
DN 51:73090
OREF 51:13199i,13200a
TI Pharmacology of carbutamide
AU Root, Mary A.
CS Lilly Research Labs., Indianapolis, IN
SO J. Pharmacol. Exptl. Therap. (1957), 119, 468-78
DT Journal
LA Unavailable
IT **119148-95-7**, Nortropine, 8-(4-phenothiazin-10-ylbutyl)- (pharmacology of)
RN 119148-95-7 CAPLUS
CN Nortropine, 8-(4-phenothiazin-10-ylbutyl)- (6CI) (CA INDEX NAME)

Relative stereochemistry.





AB Carbutamide is a sulfonylurea deriv. with low toxicity which causes hypoglycemia when given orally to normal animals. It is ineffective in alloxan-diabetic animals and in totally depancreatized dogs. If it is administered to diabetic animals being treated with insulin, their blood-glucose concns. and daily urinary sugar excretion are decreased below the levels found with insulin alone.